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Spontaneous hemothorax caused by concomitant low-dose rivaroxaban and itraconazole in a 95-year-old patient: case report and literature review

Mei Liu, Wenwen Liu and Hongmei Jiao

Abstract

Although direct-acting oral anticoagulants (DOACs) decrease the bleeding risk compared with vitamin K antagonists (VKAs), DOACs might cause spontaneous hemothorax in very elderly patients, even at a very low dose. Interactions between drugs might increase the risk of bleeding. In this article, we report a case of a 95-year-old man who developed spontaneous hemothorax while taking rivaroxaban 2.5 mg twice daily, 3 days after concomitant use of itraconazole. Rivaroxaban was discontinued, and thoracentesis was performed to drain grossly bloody pleural effusion. To our knowledge, this is the first case report of spontaneous hemothorax that might have been caused by concomitant low-dose rivaroxaban and azole anti-fungal agents. This case highlights the potential risk of spontaneous hemothorax in very elderly patients while taking rivaroxaban and azole anti-fungal agents simultaneously. Special attention should be paid to interactions between drugs that might increase the risk of bleeding. Drugs that have competing metabolic pathways should be avoided. Closer monitoring, including testing for anti-Xa and additional reassessment, should be considered in high-risk patients.

Keywords

Rivaroxaban, direct-acting oral anticoagulant, spontaneous hemothorax, concomitant medication, itraconazole, drug interaction

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Department of Geriatrics, Peking University First Hospital, Beijing, China

Corresponding author:
Hongmei Jiao, Department of Geriatrics, Peking University First Hospital, No. 8 Xishiku Street, Beijing 100034, China.
Email: jiaohongmei@sina.com

Introduction

Although the risk of major bleeding with direct-acting oral anticoagulants (DOACs) is low, spontaneous hemothorax might occur in very elderly patients with comorbidities, even at a very low dose.[1] Interaction between rivaroxaban and other medications that share a similar metabolic pathway might increase the risk of bleeding.

Case presentation

A 95-year-old man who complained of fever, cough, and expectoration was admitted to our hospital. He had a history of pulmonary infection, chronic obstructive pulmonary disease, hypertension, and hiatal hernia. Rivaroxaban was prescribed for deep vein thrombosis (DVT) 1 year earlier. Because DVT recurred after discontinuation of rivaroxaban, and no bleeding events occurred, anticoagulant therapy was prolonged after the standard 3-month therapy. The maintenance dose was adjusted to 2.5 mg twice daily after considering his age and low body mass index (BMI) of 19 kg/m^2, to reduce the risk of bleeding. He was treated with caspofungin for fungal pneumonia for 2 weeks, then with itraconazole 200 mg twice daily. Three days after beginning itraconazole, he complained of dyspnea. He spent most of the day in bed and denied any history of chest trauma. Medications upon the onset of dyspnea are listed in Table 1.

The patient's blood pressure was 105/60 mmHg, heart rate: 85 beats/minute, and respiratory rate: 25 breaths/minute with pulse oxygen saturation of 93% upon inhaling 1 L/minute oxygen through a nasal catheter. Pulmonary auscultation revealed reduced breath sounds over the left lower lung. Chest computed tomography (CT) revealed left encapsulated pleural effusion and interlobular effusion (Figure 1a). The average Hounsfield units (HU) of the pleural effusion was 25.0 Hu to 30.0 Hu. The patient's hemoglobin (Hb) level was low, at 65 g/L (normal range: 130–175 g/L); platelet count: 78×10^9 cells/L (normal range: 125–350×10^3 cells/μL); prothrombin time (PT): 17.6 s (normal range: 10.1–12.6 s); international normalized ratio (INR): 1.52; activated partial thromboplastin time (aPTT): 30.5 s (normal range: 26.9–37.6 s); and trough concentration of anti-factor Xa (anti-Xa) activity: 0.80 IU/mL. The serum creatinine level was 132 μmol/L (normal range: 44–133 μmol/L), and the serum alanine transaminase level was 10 IU/L

Table 1. List of medications at the onset of dyspnea.

Classification	Drug	Dose
Cardiovascular disease	Rivaroxaban*	2.5 mg BID
	Bisoprolol fumarate	1.25 mg QD
	Isosorbide mononitrate	30 mg QD
	Spironolactone	20 mg QD
Pulmonary disease	Itraconazole*	200 mg BID
	Tiotropium bromide	18 μg QN
	Salmeterol fluticasone	50 μg/250 μg Q12h
	Ambroxol hydrochloride	30 mg TID
Others	Ferrous succinate	100 mg TID
	Vitamin C	100 mg BID
	Esomeprazole	20 mg BID

Note: *indicates drugs that may cause drug interactions.
BID, twice daily; QD, once daily; QN, once, at night; Q12h, every 12 hours; TID, three times daily.

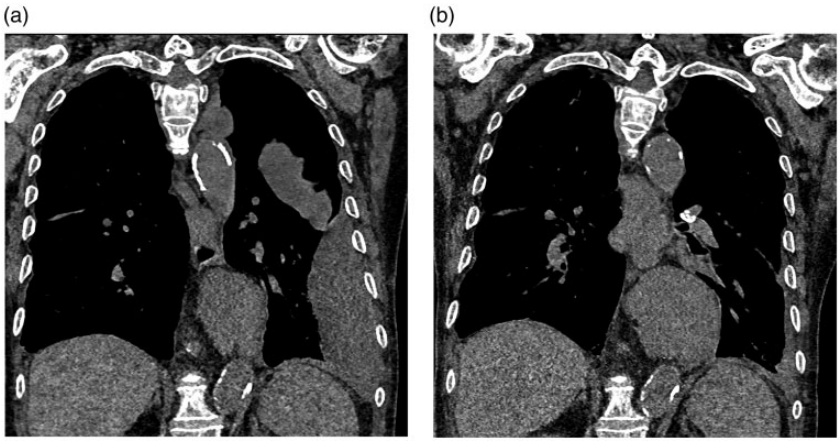

Figure 1. (a) Coronal reconstruction image of chest computed tomographic (CT) images showing left encapsulated pleural effusion and interlobular effusion (b) CT image showing that the pleural effusion resolved without new-onset pleural effusion 3 months after effusion drainage and discontinuation of rivaroxaban.

(normal range: 9–50 IU/L). In comparison, 5 days prior to the onset of dyspnea, the patient's corresponding parameters were: Hb: 79 g/L, platelet count: 85×10^9 cells/L, PT: 12.7 s, INR: 1.10, aPTT: 28.1 s, and trough concentration of anti-Xa activity: 0.07 IU/mL.

Rivaroxaban was discontinued, and 2 units of packed red blood cells and 200 mL fresh frozen plasma were transfused. Thoracentesis was performed with a 16-Fr catheter inserted after discontinuation of rivaroxaban for 24 hours. Approximately 600 mL of grossly bloody pleural effusion was drained on the first day. Dyspnea improved soon after the thoracentesis and drainage. Analysis of the pleural fluid showed a hematocrit (Hct) of 13.0% and a white blood count of 5290×10^6 cells/L. Bacterial Gram stain, acid-fast bacilli smear for tuberculosis, and bacterial culture, and cytology to detect malignant cells, were negative. Peripheral blood (PB) Hct was 24.6% on the same day, and the ratio of pleural to PB Hct was >0.5, confirming the diagnosis of hemothorax. The catheter was removed 7 days later when the daily drainage was <100 mL for 3 consecutive days. The total drainage volume was approximately 1705 mL.

Chest CT showed that the pleural effusion had resolved without new-onset effusion 3 months after effusion drainage and discontinuation of rivaroxaban (Figure 1b). When the patient was stable, the indication for anticoagulation was reassessed, and the net clinical benefit of anticoagulation was evaluated. Ultrasonography showed that there was no DVT in either lower extremity. The Padua score was 4, which indicated a high risk of venous thromboembolism. However, for this very elderly patient, the risk of bleeding outweighed the benefit of anticoagulation in the context of the recent major bleeding at an anatomically critical site. Therefore, anticoagulation was discontinued and was not reinstituted. The patient's condition remained stable, and he was discharged shortly, thereafter. The medications upon discharge are listed in Table 2.

This case report was prepared in accordance with the CARE guidelines. [2]

Table 2. List of medications at discharge.

Classification	Drug	Dose
Cardiovascular disease	Bisoprolol fumarate	1.25 mg QD
	Isosorbide mononitrate	30 mg QD
	Spironolactone	20 mg QD
Pulmonary disease	Tiotropium bromide	18 μg QN
	Salmeterol fluticasone	50 μg/250 μg Q12h
	Ambroxol hydrochloride	30 mg TID
Others	Ferrous succinate	100 mg TID
	Vitamin C	100 mg BID
	Esomeprazole	20 mg BID

QD, once daily; QN, once, at night; Q12h, every 12 hours; TID, three times daily; BID, twice daily.

Discussion

Spontaneous hemothorax is defined as pleural fluid with a pleural to PB Hct ratio of >50%, without chest trauma or procedures affecting the lung or pleural space.[3] This condition is rare in clinical practice. Anticoagulant-related spontaneous hemothorax has been reported in patients receiving heparin, warfarin, dabigatran, or enoxaparin, as a result of spontaneous rupture of small vessels.[1,4]

Cases of spontaneous hemothorax in patients receiving rivaroxaban have been reported in recent years. Four case reports were retrieved by inputting "spontaneous hemothorax" and "rivaroxaban" in PubMed (Table 3).[5–8] The ages of the patients ranged from 24 to 81 years, and three were women older than 60 years of age. The onset of the spontaneous hemothorax varied from 10 days to 4 months after taking rivaroxaban regularly. All of the cases presented with significant degrees of decreased hemoglobin, and three had elevated INR (range: 1.21–2.1). Treatments included discontinuation of anticoagulation, red blood cell transfusion, and thoracentesis. The 81-year-old patient ultimately died from septic shock, while another three patients were discharged with no observation of pleural effusion on follow-up.

Our case showed unique characteristics compared with previous published cases. First, this was a very elderly patient, with comorbidities and taking concomitant medications. Second, the patient received a very low dose of rivaroxaban (2.5 mg twice daily), which was a quarter of the recommended dose for DVT maintenance therapy. Moreover, the competing metabolic pathway between itraconazole and rivaroxaban might have increased the risk of bleeding in this case, even at such a low dose. This theory was supported by blood coagulation function test results. The trough anti-Xa activity increased significantly from 0.07 to 0.80 IU/mL, and PT increased from 12.7 s previously to 17.6 s on the day of the onset of dyspnea, 3 days after concomitant use of itraconazole. Itraconazole is a strong inhibitor of both cytochrome P450 enzyme (CYP3A4 isoform) and efflux transporter protein P-glycoprotein (P-gp).[9] Because CYP3A4 accounts for approximately 18% of total rivaroxaban elimination, and rivaroxaban is a substrate of P-gp,[10] the concomitant use of itraconazole and rivaroxaban increases rivaroxaban plasma concentrations, leading to an increased risk of bleeding. Finally, the etiology of our patient's hemothorax was diagnosed by excluding tumors and tuberculosis, and appropriate treatment led to a favorable prognosis.

Table 3. Clinical features and outcomes of the published cases of spontaneous hemothorax related to rivaroxaban.

Age/sex	Indication for anticoagulation	Dose of rivaroxaban (mg/day)	Onset of symptoms	Concomitant medications	Location of hemothorax	Bleeding in other locations	Complications	Serum creatinine (μmol/L)	INR	Outcome
78 y/F[5]	pulmonary embolism	*	dyspnea, chest pain	amlodipine, atorvastatin, fluticasone/salmeterol	left	none	*	*	1.71	discharge
24 y/M[6]	pulmonary embolism	30	dyspnea	*	left	none	shock	*	*	discharge
63 y/F[7]	atrial fibrillation	15	dyspnea, chest pain	*	right	mediastinal hematoma	*	79.6	1.21	discharge
81 y/F[8]	deep vein thrombosis	15	syncopal attack	non-steroidal anti-inflammatory drug	bilateral	hemopericardium	pneumonia, acute renal failure, septic shock	70.7	2.1	death

Note: *Not mentioned.
M, male; F, female; y, years; INR: international normalized ratio.

Hemothorax is considered major bleeding in patients taking oral anticoagulants, despite its rare occurrence. Patients and their physicians should be more aware of hemothorax as one complication of anticoagulants. Our case revealed the importance of paying careful attention to the interaction between rivaroxaban and other medications that might share similar metabolic pathways. Drugs that share competing metabolic pathways should be avoided. Anti-Xa activity is related to the concentration of oral direct factor Xa inhibitors. An anti-Xa assay is recommended in select clinical situations (e.g., renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight), and this assay is useful to prevent bleeding in high-risk patients. Closer monitoring of anti-Xa assay results and additional reassessment should be considered, especially in elderly patients with comorbidities.

Conclusion

Spontaneous hemothorax is very rare and one of the major hemorrhagic complications of DOACs in very elderly patients with comorbidities. Special attention should be paid to interactions between drugs that might increase the risk of bleeding. Closer monitoring, including anti-Xa activity and additional reassessment, should be considered in high-risk patients.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

Written informed consent was provided by the patient to have the case details and any accompanying images published. Approval by an ethics committee was not required because all data

used in this study were obtained from previous medical records.

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ORCID iD

Mei Liu https://orcid.org/0000-0003-2114-7143

References

1. Akgedik R, Günaydin Z, Bektas O, et al. Spontaneous hemothorax due to dabigatran use in a patient with atrial fibrillation. *Clin Respir J* 2017; 11: 394–396.
2. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.
3. Azfar AH, Lippmann M, Mundathaje U, et al. Spontaneous hemothorax: a comprehensive review. *Chest* 2008; 134: 1056–1065.
4. Mrug M, Mishra PV, Lusane HC, et al. Hemothorax and retroperitoneal hematoma after anticoagulation with enoxaparin. *South Med J* 2002; 95: 936–938.
5. Lee HR, Jeong YY, Lee JD, et al. Spontaneous hemothorax as an adverse effect of rivaroxaban treatment. *Turk Gogus Kalp Damar Cerrahisi Derg* 2018; 26: 309–311.
6. Yan DT, RGK H, Ng HJ. Massive spontaneous haemothorax after rivaroxaban therapy for acute pulmonary embolism. *Eur J Case Rep Intern Med* 2019; 6: 001236.
7. Yıldız İ, Aksu E, Özmen YPÖ, et al. A case of rivaroxaban associated spontaneous hemothorax. *Turk Gogus Kalp Damar Cerrahisi Derg* 2019; 27: 118–120.
8. Yu JH, Liu HH, Hsieh MJ, et al. Spontaneous bilateral haemothorax with haemopericardium secondary to rivaroxaban. *J Clin Pharm Ther* 2020; 45: 1175–1178.
9. Piérard GE, Arrese JE, Piérard-Franchimont C. Itraconazole. *Expert Opin Pharmacother* 2000; 1: 287–304.
10. Mueck W, Stampfuss J, Kubitza D, et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet* 2014; 53: 1–16.